## REMARKS

### I. Preliminary remarks

Claim 21 is amended herein. The amendment to claim 21 clarifies the claimed subject matter in reciting a term well known in the art, i.e., "heat shock response," rather than reciting a "non-mammalian" heat shock response. Claim 21 prior to amendment did recite a method in which the "non-mammalian" heat shock response occurred in a non-mammalian cell and, thus, the amendment neither alters the scope of claim 21 nor introduces new matter.

### II. The rejection of claims 21 and 22-31 under 35 U.S.C. § 112, second paragraph, has been overcome

The Examiner rejected claims 21 and 22-31 under § 112, second paragraph, for asserted indefiniteness in reciting "non-mammalian heat shock response" and in assertedly failing to define the metes and bounds of the stimulus causing it. As a preliminary matter, Applicant notes that claim 22 has been canceled, and the rejection will be addressed as applied to claims 21 and 23-31. In response, Applicant continues to disagree with the Examiner's position, as noted below. To expedite prosecution, however, Applicant has amended claim 21, the sole independent claim under examination, and thereby has effectively amended each of claims 21 and 23-31. The effective amendment to each claim under examination is to delete the "non-mammalian" modifier of "heat shock response." As amended, the claims are drawn to methods involving the induction of a heat shock response in a non-mammalian cell, and it is submitted that this was the subject matter of the claims under examination prior to the instant amendment. Accordingly, the claim amendment does not alter the scope of any of the claims under examination.

Summarizing Applicant's position that the term "non-mammalian" heat shock response was not indefinite, Applicant submits that a heat shock response was known in the art as a process comprising the expression of at least one heat shock protein. Consistent with that understanding, the application recites that "the present invention also provides a composition comprising a heat shock protein (hsp) derived from a non-mammalian eukaryote coupled to a heterologous antigenic polypeptide which composition is capable of inducing an immune response to said antigenic polypeptide in a mammal." (Specification, page 5, lines 17-20.) A method for obtaining the composition is disclosed at page 6, lines 5-9 of the

application. The two-step method involves (1) expressing the antigenic polypeptide in a non-mammalian cell subjected to a stimulus which causes the induction of a heat shock response in that cell, and (2) recovering the antigenic polypeptide coupled to one or more hsps from the cell. Further, the stimulus is defined as "a stress that is capable of initiating the production of heat shock proteins in that cell," and the expressed complex is recovered. (Specification, page 6, lines 10-20.) At page 8, lines 15-20, the application discloses that heat shock proteins are found in both prokaryotic and eukaryotic cells. In particular, the application states that "it is preferred that the hsps are derived from non-mammalian cells." Thus, a "non-mammalian" heat shock response is unambiguously defined in the application as the response of a non-mammalian cell to a stress, such as raised temperature, with that response involving the expression of at least one heat shock protein. The specification thus makes clear that it is at least one heat shock protein from a non-mammalian cell that becomes associated with an antigenic polypeptide (also being expressed in such a cell) that results in the vaccine according to the invention.

For the foregoing reasons, Applicant submits that the term "non-mammalian heat shock response" is not indefinite under 35 U.S.C. § 112, second paragraph. Applicant also submits that the rejection of claims 21 and 23-31 under § 112, second paragraph, has been rendered moot by amendment and should be withdrawn.

## III. The rejection of claims 21, 23-26, and 29-31 under 35 U.S.C. § 103(a) over Roman has been overcome

The Examiner rejected claims 21, 23-26, and 29-31 under § 103(a) over Roman, asserting that the reference taught that immunogenic peptides bound to hsp70 would be efficient in priming T-cell responses. (Office Action at page 4.) Further, one of skill would know that proteins could be expressed in *E. coli* and insect cells (e.g., with baculovirus) and that such cells have heat shock proteins. (*Id.*) Motivation to stimulate a heat shock response in a cell expressing an antigenic polypeptide would have been found in the saving of time and steps in not having to separately purify both hsp and antigen, followed by *in vitro* mixing of the two polypeptides. (*Id.*) In response, Applicant traverses.

Roman describes the formation of a complex comprising an antigenic synthetic peptide (an influenza A nucleoprotein peptide; see Roman, page 488, left column) coupled to

an isolated recombinant hsp (Mycobacterial hsp70; see Roman, page 488, left column). The method requires the synthesis of the immunogenic peptide and the isolation of recombinant hsps. In particular, a recombinant Mycobacterial hsp70 was expressed in *E. coli* and isolated by passage over ATP-agarose. In addition, the ATP-agarose-purified hsp70 was passed three times over a Detoxy –gel column to "remove any bacterial lipopolysaccharide . . . ." Roman, page 488, left column. Thus, Roman discloses a particular need to isolate the hsp70 from cellular constituents such as lipopolysaccharide. Once both components of the complex are isolated, they are incubated together, *in vitro*, to form the complex. On page 488, column 2, paragraph 3, Roman teaches the *in vitro* formation of the complex. Nowhere does Roman teach or suggest the method claimed.

In contrast to Roman, the claimed subject matter is drawn to a method whereby the expression of both the heat shock protein and the antigenic polypeptide occurs within the same cell. The *in situ* coupling of the heat shock protein and the antigenic polypeptide then occurs within the cell to form a complex comprising a heat shock protein expressed by that cell and an antigenic polypeptide expressed by that cell. As molecular chaperones (see specification, page 8, lines 4-14), moreover, heat shock proteins interact with a variety of intracellular proteins, and it was not known in the art that in such an environment, complexes would be formed between such heat shock proteins and the particular antigenic polypeptide. Consistent with this point, Roman taught isolation of hsp70 using ATP-agarose (Roman, page 488, left column), and the specification explains that ATP is used to dissociate Hsps from other proteins with which they may have associated (specification, page 11, line 30 to page 12, line 1).

Several advantages of having Hsps couple to antigenic polypeptides within the same cell, as opposed to *in vitro* coupling, are apparent. The claimed methods do not require characterization of the Hsps, such as Hsp identities or Hsp properties useful in purification. See specification, page 12, lines 8-16. The claimed methods are not limited to identified and purified Hsps and thereby maximize the opportunity for Hsp-antigenic polypeptide complex formation. Also, the induction of Hsp expression by stress facilitates the production of large quantities of Hsps, which in turn improves the opportunities for Hsp-antigenic polypeptide interaction and complex formation. See specification, page 8, line 23 to page 9, line 3. Further, at page 12, lines 14-16 of the specification, it is disclosed that the expression of

antigenic polypeptides in the presence of endogenous Hsps within a cell will lead to more efficient coupling than would be found, or perhaps even be possible, in a cell-free system. In addition, the claimed methods provide a convenient approach to the production of more than one Hsp-antigenic polypeptide complex within a cell. Co-expression of various antigenic polypeptides within a stressed cell would lead to the production of more than one complex without the difficulties of preparing such mixed compositions *in vitro* (e.g., purifying multiple antigenic polypeptides and mixing in correct proportion prior to, or after, exposure to one or more Hsps). Roman neither teaches nor suggests methods realizing these advantages of the claimed subject matter.

Furthermore, the specification teaches that the claimed method involves a cell "subjected to a stimulus which induces a heat shock protein response within the cell." The specification discloses that heat shock proteins induced following a cell stress will couple with peptides to form heat shock protein-peptide complexes that are more immunogenic than complexes formed between "unstressed" heat shock proteins and peptide fragments. See specification, Example 5, pages 66-69. Roman does not teach or suggest the induction of hsps by subjecting the cells to stress. In fact, Roman requires the use of isolated recombinant hsps. Moreover, contrary to the Examiner's assertion that one of skill would have been motivated to stress the expressing cells by heat shock to generate the complexes within the cells to save time and steps (Office Action at page 4), Roman's method cannot be modified to arrive at the claimed methods without destroying Roman's method itself. Heat shocking *E. coli* bearing a plasmid encoding Mycobacterial hsp70 would be expected to produce any *E. coli* heat shock proteins and, thus, at best, the Mycobacterial hsp70 would be found in a mixture of Hsps within the *E. coli* cell. Even such a mixture is not inherently disclosed in Roman, however, because the Mycobacterial hsp70 is being produced recombinantly and nowhere does Roman indicate that the heterologous Mycobacterial hsp70 is, or would be, responsive to *E. coli* stressors. Thus, Roman's disclosure cannot be modified to involve stressing the *E. coli* cells expressing Mycobacterial hsp70 because there is no reasonable basis for believing that the stressing would affect the expression of heterologous Mycobacterial hsp70 and, even if it did, there is no reasonable basis for believing that Mycobacterial hsp70-antigenic polypeptide complexes would effectively form in an intracellular environment rich in *E. coli* heat shock proteins.

Finally, the hsps involved in the claimed methods are native hsps, produced by the cell. Roman does not teach or suggest the use of native hsps in disclosing an isolated Hsp70 from Mycobacterium that was expressed in, and isolated from, *E. coli*. At the effective filing date of the present application, the accepted method of producing an antigenic-stress protein complex was to use recombinant hsps. It would hot have been obvious to a person skilled in the art, on reading Roman, to utilize native hsps found within the cell.

Based on the foregoing comments, Applicant submits that Roman teaches away from the claimed method in disclosing the isolation of the sole hsp disclosed in that reference, Hsp70, from bacterial lipopolysaccharide, a known bacterial toxin. In addition, there can be no suggestion to modify the teaching in Roman to stress cells expressing an antigenic polypeptide and recover complexes because Roman's method required the production of a heterologous Hsp70 that could be purified from host (*E. coli*) proteins, including host heat shock proteins. Thus, Roman neither discloses nor suggests "recovering the antigenic polypeptide coupled to one or more hsps from said cell or culture medium," as expressly recited in claim 21 and as effectively recited in dependent claims 23-31. Roman, therefore, fails to disclose or suggest each limitation of any of the claims under examination, a requirement to establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a) for the subject matter of any of those claims. In teaching away, moreover, Roman confirms that the requisite motivation to modify its teaching is, and must be, lacking, i.e., Roman cannot teach an isolated heterologous Hsp and, consistent with that teaching, be modified to arrive at the claimed method involving formation of an hsp-antigenic polypeptide complex in a host cell. Finally, Roman's failure to disclose or suggest each limitation of any of the examined claims means that Roman cannot provide a reasonable expectation of successfully arriving at the claimed subject matter. Therefore, a *prima facie* case of obviousness has not been established under § 103(a) over Roman for any of rejected claims 21 and 23-31 and the rejection should be withdrawn.

## IV. The rejection of claims 21 and 25-28 under 35 U.S.C. § 103(a) over Roman has been overcome

The Examiner rejected claims 21 and 25-28 under 35 U.S.C. § 103(a) over Roman in view of Deregt et al., Virus Res. 57:171-181 (1998) (hereinafter "Deregt"). The Examiner relied on the characterization of Roman provided in support of the rejection of

claims 21, 23-26 and 29-31, which has been addressed in Section III, above. (Office Action at pages 4-5.) Deregt was cited as assertedly teaching that BVDV is a known pathogen of bovines and that the E2 region of BVDV had been used as a subunit vaccine. (Office Action at page 5.) Concluding, the Examiner asserted that it would have been obvious to combine the immunogenic complex of Roman with the E2 peptide of BVDV disclosed by Deregt because of the economic implications arising from the disease caused by BVDV and that there would have been a reasonable expection of success in making the complex to BVDV. In response, Applicant traverses.

The reliance on Roman was misplaced because Roman neither discloses nor suggests a complex formed in a non-mammalian cell by association of at least one heat shock protein with an antigenic polypeptide, i.e., the immunogenic complex recited in the claims (see, e.g., claim 21, step (b)). In failing to teach the formation of an immunogenic complex within a non-mammalian cell, Roman also fails to disclose or suggest recovering the complex from the cell or culture medium (see, e.g., claim 21, step (c)). Under 35 U.S.C. § 112, fourth paragraph, each of dependent claims 23-31 incorporates these limitations of independent claim 21. Further, Roman cannot provide a motive to modify its disclosure because it teaches away from the claimed subject matter in disclosing the need to isolate heterologous hsp70 away from *E.*coli host materials, including lipopolysaccharide and, presumably, any *E. coli* heat shock proteins. Finally, Roman cannot provide a reasonable expectation of successfully arriving at the invention because it fails to disclose or even suggest a limitation of each of the rejected claims.

Deregt does not remedy the above-noted deficiencies in Roman as a prior art reference cited against the claims, and the Examiner has not contended otherwise. Thus, the combination of Roman and Deregt does not disclose or suggest each limitation of any of the claims under examination. Having failed to disclose or suggest each limitation of any of the rejected claims, the combination of Roman and Deregt cannot give rise to a reasonable expectation of successfully arriving at the claimed subject matter.

For the foregoing reasons, the Examiner has not established a *prima facie* case of obviousness for the subject matter of any of the rejected claims under 35 U.S.C. § 103(a) over Roman et al. in view of Deregt, and, therefore, the rejection should be withdrawn.

## V. Conclusions

For all of the foregoing reasons, Applicant submits that each of the rejections of claims 21 and 23-31 has been overcome and the claims are now in condition for allowance. The Examiner is invited to contact the undersigned at the telephone number listed below in order to discuss any remaining issues or matters of form that will move this case to allowance.

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Respectfully submitted,

By _____

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